DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	4/22/2019-5/3/2019*
	FEI NUMBER 3002984011

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Umesh Kumar Gupta, Campus Head

FIRM NAME	STREET ADDRESS
Cadila Healthcare Limited	419 & 420 8a Village-Moraiya
CITY, STATE, ZIP CODE, COUNTRY Ahmedabad, Gujarat, 382210 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Equipment and utensils are not cleaned and maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

1. Residues were observed on surfaces of cleaned (b) (4) equipment. Cleaning procedures do not include provisions for routine cleaning or inspection of the (b) (4) duct area.

   a. Non-dedicated (b) (4) equipment CH/TS/013 had residues in the (b) (4) duct and on the back of the (b) (4) on April 24, 2019. The equipment was identified as clean. This (b) (4) equipment has been used in the manufacture of tablets with (b) (4) active ingredients including (b) (4) . Tablet batches of (b) (4) , (b) (4) , and (b) (4) manufactured on this equipment have been distributed to the US market.

   b. Non-dedicated (b) (4) equipment CH/MC/TAB/1999/19 had residues in the (b) (4) duct and on the back of the (b) (4) on April 24, 2019. QC testing detected the presence of the following APIs in the residue: (b) (4) , (b) (4) , (b) (4) , (b) (4) , (b) (4) , (b) (4) , (b) (4) , (b) (4) , (b) (4) , (b) (4) , and (b) (4) . This (b) (4) equipment has been used to

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	Justin A Boyd, Investigator - Dedicated Drug Cadre Thomas J Arista, National Expert Rita K Kabaso, Office of International Programs Employee	X Justin A Boyd Investigator - Dedicated Drug Cadre Signed By: 2000358686 Date Signed: 05-03-2019 10:40:56	5/3/2019

manufacture tablet products for the US market including, but not limited to: (b) (4), (b) (4), (b) (4), and (b) (4).

c. Non-dedicated (b) (4) equipment CH/MC/TAB/2009/333 had (b) (4) residues on the back of the (b) (4) of the (b) (4) duct on April 24, 2019. Additionally, (b) (4) particles were observed on the front side of the (b) (4) and on surfaces in the (b) (4). The equipment had been cleaned and the previous product manufactured was (b) (4) tablets, a (b) (4) product. This (b) (4) equipment has been used to manufacture tablet products for the US market including, but not limited to: (b) (4), (b) (4), and (b) (4).

d. Non-dedicated (b) (4) equipment CH/PM/013 had white colored residues in the (b) (4) duct (b) (4) on April 24, 2019. The equipment had been cleaned. This (b) (4) equipment has been used to manufacture tablet products for the US market including, but not limited to: (b) (4), (b) (4), and (b) (4).

e. Further investigation conducted by the quality unit identified visible traces/stains/smear/powder in the (b) (4) duct or (b) (4) on cleaned (b) (4) equipment CH/MC/TAB/1999/27, CH/MC/TAB/2004/176, CH/MC/TAB/1999/11, CH/TT/005, CH/TF/004, CH/TE/071, CH/PP/082, and CH/PG/014. These pieces of equipment were non-dedicated and used to manufacture tablet products for the US market.

2. Two (b) (4) stopper bowls used on parenteral filling line (b) (4) were observed to have unsmooth (b) (4) stopper contact surfaces, including scratches and dents. Both stopper bowls were tagged as clean and wrapped for entry into the aseptic processing area on April 29, 2019. Each contained black residues that could be removed with further wiping.

3. The (b) (4) chute that is used during the manual transfer of the sterile (b) (4) stoppers during the aseptic filling process appears to have some form of visible scoring on the (b) (4) surface, there are several dents on the (b) (4) body and the chute's inlet and outlet ports have rough and uneven edges that are not smooth, cleanable surfaces.

4. Manufacturing equipment including (b) (4) were observed to contain visible dents on the exterior and interior surfaces of the equipment. A mallet is used on the exterior surface of the (b) (4) to remove drug product adhered inside the (b) (4).

OBSERVATION 2

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and followed.

1. Procedure 0301-SOP-MFG-00506 "Guidelines for Working in Aseptic Area" requiring operators to not lean over sterilized containers or closures and not to obstruct laminar air flow was not followed:

    a. During stopper addition for (b) (4) injection batch (b) (4) on April 22, 2019, the operator passed their hands over the opened bag of sterile stoppers during bag (b) (4) and handling. When the stoppers were poured into the stopper chute, the operator's hands were over the sterile stopper chute.

    b. During filling of (b) (4) injection batch (b) (4) there were six interventions to remove a fallen vial at the (b) (4) vial (b) (4). During the intervention, the operator used the restricted access barrier system (RABS) (b) (4) to reach over open, sterile vials at the vial (b) (4). These vials were not cleared. The

Non-(b) (4) Quality Assurance Deputy General Manager confirmed the (b) (4) are not sterile and operators are permitted to use the (b) (4) above empty sterile vials without requiring the need to clear the vials.

2. During the aseptic filling operations performed in Fill Line (b), we observed personnel enter into and out of the Grade A area via the (b) (4) glass vial conveyor that is positioned subsequent the glass vial stoppering process (Note: there is a similar glass vial conveyor system for Fill Line (b) & (b)). We observed this activity on numerous occasions with the (b) (4) RABs access (b) (4) remaining open for approximately 3 to 4 minutes at a time. There is no SOP and/or language in the manufacturing batch record to describe and establish the manner of how personnel access and personnel activities are to be performed while in the Grade A conveyor area.

OBSERVATION 3

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile did not include adequate validation of the aseptic process.

Regarding the aseptic processing simulation of the (b) (4) process, not all media filled vials are subject to the (b) (4) steps in that the media filled vials that are exposed during the fill room operators' manual interventions are removed from the batch of the media filled vials. In addition;

1. The media filled vials that are removed during the manual interventions and culled from the media filled batch and are not subject to the routine aseptic filling process. For example, media fill batch number (b) (4) dated January 16, 2019 documents the removal of 1,328 media filled vials. The production operator and Senior Executive explained that the 1,328 media filled vials were placed on a collection (b) (4) under LAF conditions, which is the location where the (b) (4) stoppers are (b) (4), manually, on the glass vials. Following the manual process of

(b) (4) the (b) (4) stoppers on to the media filled vials, they are transferred to an (b) (4) that feeds into the vial (b) (4) station. The aforementioned manual operations and processing steps are not part of the routine aseptic filling process for (b) (4) finished drug products;

2. The above practice is commonly performed for all media fill simulations performed in (b) (4) Facility (b) e.g.

Batch number	*Container*	*Date of Mfg.*	*# of culled units*
(b) (4)	(b) (4) ml (b) (4) USP (b) (4) (b) (4) Glass vials	(b) (4)	881
(b) (4)	(b) (4) ml (b) (4) USP (b) (4) (b) (4) Glass vials	(b) (4)	1354
(b) (4)	(b) (4) ml (b) (4) USP (b) (4) (b) (4) Glass vials	(b) (4)	652
(b) (4)	(b) (4) ml (b) (4) USP (b) (4) (b) (4) Glass vials	(b) (4)	737
(b) (4)	(b) (4) ml (b) (4) USP (b) (4) (b) (4) Glass vials	(b) (4)	1292
(b) (4)	(b) (4) ml (b) (4) USP (b) (4) (b) (4) Glass vials	(b) (4)	1262
(b) (4)	(b) (4) ml (b) (4) USP (b) (4) (b) (4) Glass vials	(b) (4)	1332

OBSERVATION 4

Aseptic processing areas are deficient regarding air supply that is filtered through high-efficiency particulate air filters under positive pressure.

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1. The Airflow Visualization Test Protocol cum Reports (aka smoke studies) acceptance criteria includes "(b) (4) turbulence should be observed. Laminar visible smoke / air flow should be maintained inside the LAF. The visible smoke / air should move from the working zone to outside area." And, regarding the acceptance criteria during the material transfer from the (b) (4) zone to (b) (4), (b) (4) to filling room and (b) (4) zone to filling room, is as follows. The visible smoke / air should move from more critical area to less critical areas immediately while opening the (b) (4). However, there are a number of instances where either the personnel activities and/or production related equipment block the ability to view the laminar air flow, for example, the video does not capture when personnel are removing the stoppered vials out of the (b) (4), the personnel activities impact upon the laminar air flow, or the impact on the laminar air flow when moving equipment. In addition:

   a. The air flow pattern evaluations for line (b) (4) demonstrated air flowing (b) (4) the stopper addition chute and creating turbulence where the laminar flow (b) (4) the stopper addition air meets with the air flowing (b) (4) of the stopper chute.

   b. The air flow pattern evaluations did not include an assessment of the air flow when manually transferring the (b) (4) media filled glass vials from the fill line to (b) (4) 2.

   c. There is no air flow pattern evaluation performed to determine the impact upon the laminar airflow during the movement of the mobile transfer unit from the (b) (4) zone to (b) (4).

   d. There is no air flow pattern evaluation performed to ensure that the movement of HEPA filtered air from the Grade B does not enter into the Grade A (b) (4) area.

   e. There is no air flow pattern evaluation for the routine intervention of removing fallen vials at the vial (b) (4) using the RABS (b) (4).

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2. The air pressure differential readings are obtained (b) (4) during the (b) (4) manufacturing (b) (4). For example, a production operator explained the air pressure readings are taken at the (b) (4). However, there are no air pressure measurements taken during a dynamic state of manufacturing operations. In addition;

   a. Analog (b) (4) gauges are used to measure/monitor the air pressure differentials between the controlled and classified manufacturing areas. The individual (b) (4) gauges are not connected (e.g., computer based system) in a manner to collectively monitor all of the air pressure differences in a dynamic state of operation. The manner of monitoring real time air pressure differentials via the use of the analog (b) (4) gauges during routine manufacturing operations in the controlled and classified manufacturing areas is not current good manufacturing practice technology.

   b. There is no record to document the mm of water column air pressure differentials are maintained during routine aseptic filling operations to demonstrate that the requisite air pressures (e.g., (b) (4) positive air pressure to less positive or negative air pressures) are appropriately sustained.

   c. There are (b) (4) transfer (b) (4) used to move material into and/or out of the controlled and classified manufacturing areas. The transfer (b) (4) without an air flow unit (aka static (b) (4) and do not (b) (4)) do not have an air pressure monitoring device (e.g., analog/digital gauge) and there is no record to document that the appropriate air pressures are maintained i.e., the lesser quality of air (non-classified) does not ingress into the controlled and classified manufacturing areas.

3. On filling line (b) (4), the stoppered filled glass vials are conveyed under Grade A conditions following the aseptic filling as they travel to the vial capping station located in room # (b) (4) (Grade C). As the stoppered vials enter the capping station the they are no longer in a Grade A environment. Rather, the Senior Manager Quality Assurance explained that the air is intended to

be unidirectional with no specific classification of the air;

There is no scientific rationale to support not maintaining the stoppered glass vials under Grade A conditions prior to the capping process.

OBSERVATION 5

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

f. The EM trend data documents recurring microbial contamination via the personnel monitoring program. The EM data reveal certain individuals who appear to be a source for the Bacillus and Pseudomonas microbial contamination in the Grade B and Grade A manufacturing areas. The data shows the Grade B corridor used to access fill lines (b) (4) and (b) (4) may be a route of contamination to the Grade A areas. Effective actions have not been taken to address these recurrences.

g. Thorough assessments to establish rationale for viable environmental monitoring limits, frequencies, and locations have not been documented. For example, the assessments lack documented rationale for the following:

   a. The personnel working with their body (b) (4) inside of the Grade A stopper addition area aseptically open bags of sterile stoppers and add sterile stoppers via a sterilized chute. The operator is held to Grade B limits during personnel monitoring. This allows for (b CFU on the operators hands without requiring any additional action.

   b. There is no viable air monitoring via settle plates or active air sampling of the Line (b) (4) Grade A conveyor area (b) (4) the stoppering station and the capping room. A surface

monitoring sample is taken in this area (b) (4) per (b) (4), although filling can occur up to (b) (4) a (b) (4). Personnel move through this area with their (b) (4) body in the Grade A area and the barrier (b) (4) were observed to remain open to the Grade B areas for approximately 3-4 minutes.

c. Monitoring of sterilized tools including the (b) (4) used for aseptically opening stopper bags, the sterile rod for removing stuck stoppers, and the sterile forceps for removing fallen or jammed stoppers and vials are only conducted (b) (4) per (b) (4). Batches could be filled up to (b) (4) times per (b) (4). Additionally, there are (b) forceps located in the Grade A filling barrier and the personnel performing monitoring chooses one forceps at random. They do not document which forceps is chosen for sampling.

d. Viable air monitoring in the Grade A (b) (4) zone where the (b) (4) is unloaded and filling machine parts are stored is Grade A is only conducted (b) (4) per (b) (4).

e. Procedures and environmental monitoring records lack descriptions of the locations to be sampled. For example, the Grade A (b) (4) in the stopper addition is to be monitored, but the location is chosen at random. Sampling of Grade B floors and walls is done at random. The location chosen is not documented.

h. Non-viable particle (NVP) measurements are taken in the Line (b) (4) Grade A glass vial conveyor area (b) (4) the stoppering station and the capping room. However, the NVP probe is located (b) (4) (approximately (b) (4)) away from the personnel access area and the NVP data does not accurately reflect the NVP levels when personnel enter and/or exit the Grade A glass vial conveyor area.

i. NVP measurements are taken during routine aseptic filling process of the (b) (4) drug

products via the use of stationary and mobile portable NVP monitoring equipment. During the loading of the (b) (4) glass vials into the (b) (4) the NVP measurements are obtained (i.e., "(b) (4) batch (b) (4) per (b) (4) during the loading" of the (b) (4)) via the use of portable mobile NVP monitoring equipment. However, the batch manufacturing records (BMR) do not document the time (as confirmed by Manager Quality Assurance) when the NVP measurements are taken during the loading of the (b) (4) glass vials into (b) (4) to corroborate and ensure that the (b) (4) open vials are maintained in a Grade A environment. In addition:

a. The "Monitoring of Non Viable Particles Count" document # SOP MFG-01153 instructs to "Take the particle count under the HEPA filter and are at operational height …". However, the SOP is silent with respect to establishing the manner of how the NVP probe should be positioned; and,

b. The SOP is deficient with regards to establishing what specifically constitutes an "operational height" and there is no specific description of where exactly the NVP monitoring should take place in the (b) (4) Grade A area.

j. In (b) (4) the (b) (4) aseptically filled glass vials are manually transferred from the filling equipment to the (b) (4) via the use of a (b) (4) Semi-Automatic (b) (4) Loading Trolley. The NVP isokinetic probe ((b) (4)) is positioned approximately (b) (4) (approximately (b) (4)) from the mobile trolley's HEPA filter face. The NVP probe is not positioned or located near the work surface. Rather, the isokinetic probe is positioned such that the top of the (b) (4) is approximately (b) (4) (approximately (b) (4)) away from the (b) (4) vials;

During the qualification of the semi-automatic loading trolley, the Senior Manager Quality Assurance, explained that the NVP measurements were obtained via the use of a mobile particle counter. However, the location and/or placement of the isokinetic probe is unknown.

OBSERVATION 6

The production area air supply lacks an appropriate air filtration system.

The Vice President Projects & Engineering described the "As Built" diagrams for HVAC reflect all changes made in the specification and working diagrams during the construction process, which include the exact dimensions, geometry and location of all elements of the work. However, there are no "As Built" engineering diagrams for the air handling units that supply air into Fill Lines #(b) (4) and (b) (4) manufacturing facilities that are used to manufacture aseptically filled finished drug commodities. In addition;

4. There are approximately (b) (4) air handling units in the approximate (b) (4) square meter building that contain the aseptic filling lines in the parenteral and (b) (4) manufacturing facilities. The building also houses, for example, the manufacturing operations for the tablet, aerosol, (b) (4) and (b) (4) capsules, (b) (4) and (b) (4) operations. Notwithstanding the aseptically filled sterile and (b) (4) injectables, there are (b) (4) pharmaceutical commodities that are manufactured in tablet facility (b) (4), tablet facility (b) (4), and (b) (4). The (b) (4) drugs and (b) (4) are summarized as follows;

Medicinal Products	(b) (4)
(b) (4)	

There are no "As Built" engineering diagrams to ensure that the return air from the production areas that are used to manufacture the (b) (4) drugs do not enter and/or connect to the air ducts for the air handling unit used for the aseptic filling processes;

5. There is an "As Built" engineering diagram for the (b) (4) air ducts, that is, diagram #TTT-DRG-0506-46-03 dated 11.02.06. The Head of Non-(b) (4) Quality Assurance Deputy General Manager confirmed that the individuals that reviewed and approved the "As Built" diagram no longer work at the company and the current Quality Unit has not reviewed and approved the 11.02.06 dated "As Built" diagram for the (b) (4) operations.

OBSERVATION 7

Failure to maintain a backup file of data entered into the computer or related system.

Regarding the (b) (4) process, the SCADA (Supervisory Control and Data Acquisition) computer system monitors and controls the (b) (4) processing parameters and should there be aberrant events (e.g., process failure, PC failure, instrument failure, device failure, device state failure and/or utility failure) the computer based systems electronically captures the alarmed events. The (b) (4) operator explained that the data that is captured by the SCADA is retained for approximately 6-months

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(Note: the computer's memory capacity is (b) (4) GB). For example, the (b) (4) operator demonstrated by displaying all the currently retained (b) (4) data, which is only as far back as October 28, 2018 to the present (April 29, 2019). In addition:

k. On January 5, 2019, deviation DC/2019/014 was initiated due to (b) (4) ((b) (4)) computer monitor and CPU breakdown observed during (b) (4) of (b) (4) Injection (b) (4) mg/vial injection batch no. (b) (4). Due to the breakdown the (b) (4) report was not generated (b) (4) and (b) (4) for (b) (4) CPU has a storage capacity of (b) (4) GB which provides six (6) months of original data storage. Original trending data for alarms could not be recovered as the system is not backed-up. Prior to January 5, 2019, alarm trending data and system audit trail data could not be provided for review.

   Deviation DC/2019/014 was closed and approved on February 1, 2019 by the Plant Head, Quality Assurance. Your Corrective and Preventative Action was to install an external hard drive. The (b) TR external hard drive for (b) (4) purchase order is dated April 15, 2019. This is approximately 73 days after Deviation DC/2019/014 was closed and 100 days after your (b) (4) PC data crashed. You could not provide justification for the time-lapse between deviation occurrence and external drive purchase.

l. The General Manager Quality Assurance confirmed that they do not track or trend the (b) (4) process aberrant alarm events that are captured by the SCADA computer based system.

m. The "Computer System Validation Master Plan" document #CQA/CSVMP/00 dated 01/12/15 "…provides guidance and typical approach to validate a computerized system. It also serves as a resource for development of specific computer system validation project plans." In addition, the Computer System VMP establishes and provides guidance regarding for example, "…Back-up and restoration policies are in place and effective for Operating software, application software, configuration settings and data and are getting backed up on an external or any certified media to

ensure access if on-line records are lost either through accidental deletion or equipment problems." The (b) (4) equipment operator, the Senior Executive and Quality Assurance confirmed that they currently do not have the capacity to back up the electronic data that is captured by the (b) (4) SCADA system.

n. A (b) (4) process report is printed out subsequent the routine (b) (4) process, which includes printing out a color coded graphical representation of the (b) (4) process. The (b) (4) equipment operator, the Assistant Manager and Quality Assurance explained that they perform a "verification and confirmation" of the (b) (4) processing data. As an example, with the Vice President of Injectable Operations and Quality Assurance it was calculated that there are approximately (b) (4) data points summarized in the digital print out. However, there is no specific language in the standard operating procedure (SOP) to establish the content of the verification and confirmation process (i.e., what specific process data is verified and confirmed).

o. The "Rights of authorization level" lists the personnel who are allowed access to the (b) (4) computer. Of the (b) (4) individuals that are listed as "active", 9 individuals no longer work for the company or have moved to other departments.

OBSERVATION 8

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

1. Investigations into failures during periodic qualification of the terminal sterilization cycles did not identify assignable root causes for failures to requalify the previously validated cycle parameters.

a. Investigation DC/2018/381 did not establish an assignable cause for failure during the periodic requalification of (b) (4) Injection (b) ml in (b) ml vial. During periodic qualification of load (b) (4) (minimum load) it was noted that the required (b) (4) was not achieved in (b) (4) number (b) (4) and (b) (4) during the cycle and there were (b) (4) fluctuations observed in (b) (4) and (b) (4). The investigation DC/2018/381 states: "based on the discussion with CFT teams, cycle parameters for Load-(b) (4) was changed for (b) (4) from (b) (4) for (b) (4) to (b) (4) for (b) (4), which is more efficient for (b) (4) and (b) (4) time (b) (4) the sterilization (b) (4) to have (b) (4) and (b) (4) during sterilization cycle because (b) (4) have more (b) (4) time during (b) (4) phase". However, the investigation does not identify an assignable cause for why the previously validated cycle parameters could not be requalified.

b. Investigation DC/2017/580 did not establish an assignable cause for failure during the periodic requalification of (b) (4) Injection USP (b) ml in (b) ml vial. During periodic qualification of load (b) (4) (minimum load) the required (b) (4) was not achieved in (b) (4) numbered (b) - (b) (4).

c. Investigation DC/2017/736 did not establish an assignable cause for failure during the periodic requalification of (b) (4) Injection (b) (4) ml in (b) (4) ml vial. During periodic qualification of load (b) (4) (minimum load) the minimum sterilization (b) (4) time of (b) (4) (b) (4) was not achieved for (b) (4) numbered (b) - (b) (4).

2. (b) (4) tablets (b) (4) g process validation was approved on 07/12/2017. After approval, 18 consumer complaints have been documented regarding Organopathy ((b) (4) smell). Of the 18-consumer complaint documented, 0 retain or complaint return samples were tested for (b) (4) (b) (4). Complaint investigation included opening of the retain lot and smelling the retain lots

for (b) (4) smell. Per your findings, (b) (4) smell was observed in retain and complaint returned samples. However, no analytical testing was conducted. Additionally, you failed to verify whether (b) (4) used in the formulation containing complaint batches was used in other drug products which resulted in Organopathy ((b) (4) smell).

You determined Organopathy ((b) (4) smell) is due to the bottle headspace area. You did not conduct a risk assessment to determine whether other products having Organopathy ((b) (4) smell) complaints have the same/similar headspace range.

OBSERVATION 9

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

p. (b) (4) Tablet (b) (4) g (b) (4) ((b) (4)) variability has not been assessed within a batch and between batches. Currently, (b) (4) batch of (b) (4) Tablet (b) (4) g is (b) (4) and (b) (4) for (b) (4) at your fixed (b) (4) range. Per your Sr. Vice President Corporate Quality Assurance, (b) (4) testing has been exempted from routine testing based on process validation batches. Your established (b) (4) (b) (4) parameter is NMT (b) (4) ppm. Refer to the table below for examples of (b) (4) data obtained during (b) (4) process validation:

(b) (4) batch	(b) (4)
(b) (4)	
(b) (4)	
(b) (4)	
(b) (4)	

Data demonstrating that your current (b) (4) process effectively and consistently (b) (4) from different locations of the (b) (4) was not included in process validation studies. According to your (b) (4) consumer complaint (b) (4) C-0301-2018-0002 initiated on January 10, 2018 regarding Organopathy ((b) (4) smell), your investigation indicated that the most probable cause for the (b) (4) smell in (b) (4) is due to the use of (b) (4) in your formulation.

q. (b) (4) Tablet (b) (4) g validated hold time studies are not representative of your current manufacturing process. Hold time validation for (b) (4) was conducted by dispensing (b) (4) (b) (4) batch (b) (4) in (b) (4) containers with net weight varying between (b) (4) to (b) (4). (b) (4) g was obtained from each container using a (b) (4) and placed in a (b) (4) and (b) (4) container. Hold time study was conducted from the (b) (4) g sample over (b) (4) period. There is no scientific justification demonstrating that product (b) (4) in the (b) (4) g study sample is equivalent to the (b) (4) or (b) (4) storage container. In addition, your sampling plan for (b) (4) does not evaluate variability within a batch or between batches. The following parameters were tested for (b) (4): (b) (4).

(b) (4) Tablet (b) (4) g validation for hold time study for compression is not representative of the manufacturing process. (b) (4) tablets were obtained from (b) (4) tablet batch size for compression hold time. Samples were kept over (b) (4) period after compression and evaluated for (b) (4). Your current sampling plan does not evaluate for variability within a batch. Total hold time from manufacturing to packaging has been established for no more than (b) (4).

r. Production personnel are permitted to set the compaction force reject limits outside of the limits established in the batch records without requiring a documented justification or evaluating the impact on the validated process. Tablet compaction force reject ranges are established during process validation batches and the subsequent (b) (4) commercial batches. The compaction force can

be impacted based on variability on the (b) (4) properties.

For example, the established batch record limit for (b) (4) tablet batch (b) (4) was (b) (4) KN to (b) (4) KN. The actual range used for the (b) (4) of the compression machine was (b) (4) KN to (b) (4) KN and the (b) (4) was (b) (4) KN to (b) (4) KN. The batch record limit established for (b) (4) tablet batch (b) (4) was (b) (4) KN to (b) (4) KN, but the actual range used was (b) (4) KN to (b) (4) KN.

OBSERVATION 10

The responsibilities and procedures applicable to the quality control unit are not fully followed.

1. Closed Circuit Television Cameras (CCTV), DVR & Monitoring Screens were installed for the parenteral facility Fill Lines (b) (4) and (b) (4) Facility (b) (4). As described in the change control documents CC/15/EG/044 dated April, 27, 2015 and CC/15/EG/066 dated August 10, 2015, the reason/justification for change is "To keep close watch on production practices and upgrading the facility". The installation and operational qualifications (I/OQ) for lines (b) (4) were performed on August 2015; for lines (b) (4) in September 2015 and for the (b) (4) Facility (b) (4) the CCTV I/OQ was performed on May 2015. Some of the key functional checks performed during the I/OQ include but not limited to Startup of the DVR, Shutdown of the DVR, Locking the DVR, and Status Checking of the DVR. Despite the installation and operation of a digital video recorder, the Head of Non-(b) (4) Quality Assurance Deputy General Manager explained that they do not record the production operations. In addition:

    a. The Head of Non-(b) (4) Quality Assurance Deputy General Manager explained that they video record all aseptic processing simulations (aka media fills) via the use of a small video camera and tripod positioned and located outside of the fill rooms; the video

recording is taken from a viewing window (approximately (b) (4) x (b) (4)) in the personnel corridor. Regarding (b) (4) fill line, there are a number of objects that prevent from having an unobstructed view of the aseptic processing simulations. For example, the fill equipment, the fill equipment (b) (4) , the size and movement of the mobile transfer trolley, as well as, the personnel activities performed in the Grade A and Grade B areas, present limitation with regards to observing the aseptic process, which is further hindered by the location of the video camera and physical limitation of the viewing window;

b. There is a CCTV system with a video camera that provides the ability to observe the Grade A and Grade B areas in front of (b) (4) 2 without the aforementioned obstructions. However, the Head of Non-(b) (4) Quality Assurance Deputy General Manager explained that they do not use the CCTV to record the aseptic media filling process; and,

c. The CCTV system has a video camera to observe various aseptic filling operations in Fill Line (b). However, one of the cameras is positioned in a manner such that the structure of the filling equipment obstructs the ability to observe the aseptic filling operations.

2. The protocol and report regarding the personnel "Aseptic Area/Clean Room Garments Qualification Study After Maximum Sterilization Cycle (Start From Washing, Drying, Sterilization and Usage) document # OS/VP/610 dated March 08, 2016 is used to supports and "…recommends the use of personnel garments up to (b) (4) washing, drying and sterilization cycle and usage for routine commercial purpose." Evaluations and determinations of the garments are performed via a German company vendor. For example, determinations of the following i.e.,

- (b) (4) ((b) (4));
- (b) (4) ((b) (4) : (b) (4));
- barrier ability against airborne particles ((b) (4) -method; (b) (4));

- pore size ((b) (4));
- particulate contaminant by (b) (4) Method ((b) (4) -method according to (b) (4) ((b) (4)); and,
- particulate contaminant by (b) (4) ((b) (4)).

Despite the establishment of standard operating procedures regarding vendor qualification for excipients and qualification for API, a similar consideration was not performed for the German contract vendor. In addition:

a. There is a current "Qualification of Service Provider" document #SOP-CQ-00058 dated January 09, 2018. Corporate Quality Assurance confirmed that the company has not retrospectively performed a vendor audit of the contractor noted above;

b. The biological indicators (BI) used in support of the (b) (4) sterilization process are purchased from an outside vendor. However, Corporate Quality Assurance confirmed that they have not performed a vendor audit of their BI supplier.

3. The firm uses a Building Management System (BMS) to monitor the temperature, percent relative humidity and air pressure differences between the Class D glass washing room and the Grade B aseptic filling suites. The BMS installation and qualification (I/OQ) is dated December 17, 2008. The Head of Non-(b) (4) Quality Assurance Deputy General Manager confirmed that the individuals that reviewed and approved the I/OQ documents no longer work at the firm and the current Quality Unit has not reviewed and approved the 2008 I/OQ documents.

OBSERVATION 11

Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	4/22/2019-5/3/2019*
	FEI NUMBER 3002984011

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Umesh Kumar Gupta, Campus Head

FIRM NAME	STREET ADDRESS
Cadila Healthcare Limited	419 & 420 8a Village-Moraiya
CITY, STATE, ZIP CODE, COUNTRY Ahmedabad, Gujarat, 382210 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

1. SOP-QC-00055 "Investigation of Extraneous Peaks Observed During Chromatographic Analysis" is not applied to raw materials received from vendors. The chromatograms have not been evaluated for extraneous unknown peaks. For example, during residual solvent testing of (b) (4) #(b) (4) there was a peak at approximately (b) (4) that was not further evaluated.

2. Method QC/STP/I/2252-03 was not followed in analysis of (b) (4) tablets for (b) (4) (b) (4) by gas chromatography. The method requires the standards be prepared with (b) (4). During the preparation of standards for sequence QC863VEN1606A, the standards were prepared with both (b) (4) and (b) (4), so the same standards could be used to evaluate (b) (4) tablets for (b) (4) and (b) (4) tablets for (b) (4). The (b) (4) and (b) (4) peaks co-elute, potentially reducing the accuracy of the standard area count compared to the approved method.

3. Per your "Operation, Calibration and Data Acquisition of Online Data Logger" SOP 0301-SOP-QC-00240, incidents will be generated for investigation for incubator temperature excursions of (b) (4) or more. No sound justification was provided for the (b) (4) limit as it is not representative of your incubator historical temperature excursions.

OBSERVATION 12

In-process specifications are not determined by the application of suitable statistical procedures where appropriate.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Justin A Boyd, Investigator - Dedicated Drug Cadre Thomas J Arista, National Expert Rita K Kabaso, Office of International Programs Employee	X Justin A Boyd Investigator - Dedicated Drug Cadre Signed By: 2000358686 Date Signed: 05-03-2019 10:40:56	5/3/2019

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	4/22/2019-5/3/2019*
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CITY, STATE, ZIP CODE, COUNTRY Ahmedabad, Gujarat, 382210 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

There is no documented rationale to explain how the critical, major, and minor limits for rejected parenteral vials during visual inspection are established. Sources of commonly observed major defects have not been further investigated, including high volume vials, low volume vials, or vials with fibers.

OBSERVATION 13

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

Sterile wipes used during cleaning of equipment in the ISO5 and ISO7 aseptic filling lines, intended to remove particles from equipment surfaces, were observed to contain loose fibrous threads.

OBSERVATION 14

Master production and control records lack complete manufacturing and control instructions.

The (b) (4) process for Fill Line (b), during routine aseptic filling and the aseptic process simulation, the (b) (4) microbial growth media is transferred to a sterilized (b) (4) holding vessel in room (b) (4) (Grade B). A production room operator confirmed there is no written standard operating procedure, and/or in the BMR, that specifically describes and establishes that the (b) (4) tubing is to be manually transferred from the Grade B area into the Grade D room.

*DATES OF INSPECTION

4/22/2019(Mon), 4/23/2019(Tue), 4/24/2019(Wed), 4/25/2019(Thu), 4/26/2019(Fri), 4/29/2019(Mon), 4/30/2019(Tue), 5/01/2019(Wed), 5/02/2019(Thu), 5/03/2019(Fri)

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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Umesh Kumar Gupta, Campus Head

FIRM NAME	STREET ADDRESS
Cadila Healthcare Limited	419 & 420 8a Village-Moraiya
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Ahmedabad, Gujarat, 382210 India	Drug Manufacturer

X Thomas J Arista
National Expert
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Date Signed: 05-03-2019 10:41:25

X Rita K Kabaso
Office of International Programs Employee
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DATE ISSUED
5/3/2019